Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3525-3528, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0621-4

Silver-Catalyzed Heterocyclization : First Total Synthesis of the Naturally Occurring *cis* 2-Hexadecyl-3-hydroxy-4-methylene Butyrolactone

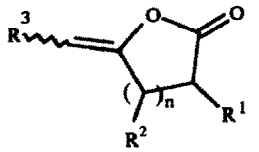
V. Dalla, P. Pale*

Laboratoire de Chimie Organique Physique, Associé au CNRS,
U.F.R. Sciences, B.P. 347, 51062 REIMS, France

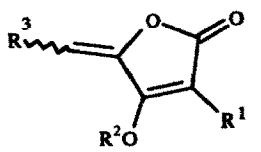
Key Words : silver-catalyzed cyclization , γ- alkylidene γ- lactones, exocyclic enol lactones, 3-hydroxy-4-methylene butyrolactones, β- hydroxy-γ- acetylenic acids.

***Abstract** : The title compound was obtained in 4 steps with an overall yield of 64% with the silver-catalyzed cyclization of the corresponding substituted β- hydroxy-γ- acetylenic acid as the key-step.*

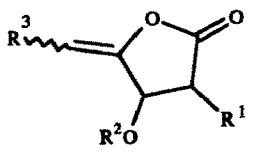
Exocyclic enol lactones (Scheme 1) represent a common moiety shared by a number of natural products exhibiting biological activities. The γ- alkylidene γ- lactones bearing an oxygen atom in the β position, i. e. tetronic acid derivatives and their dihydro analogs (Scheme 1),[1] are the most widely distributed among these naturally occurring compounds. Although antibiotic properties are usually associated with these structures, ichtyotoxic and insecticidal activities have been attributed to some of these compounds. Furthermore, extracts now known to contain such exocyclic enol lactones were actually used in traditional medicine.[2]



exocyclic enol lactones



γ -alkylidene tetronic acids

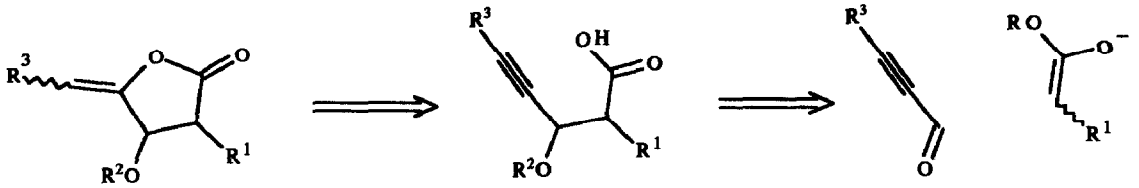


γ -alkylidene dihydrotetronic acids

Scheme 1

In connection with our ongoing program devoted to the synthesis of oxygenated heterocycles,[3-7] and due to their biological properties, we became interested in developing a general and mild access to γ- alkylidene dihydrotetronic acids. As we recently showed that silver carbonate is an efficient catalyst for the cyclization of acetylenic alcohols and acids,[3] we reasoned that β- hydroxy-γ-alkylidene-γ- lactones and their derivatives would

be readily accessible via the silver-catalyzed cyclization[8] of β-hydroxy-γ-acetylenic acids. The most convergent route toward these acetylenic acids would be an aldol condensation between the appropriate acid or ester and the properly substituted propargyl aldehyde. This sequence is retrosynthetically outlined in Scheme 2.

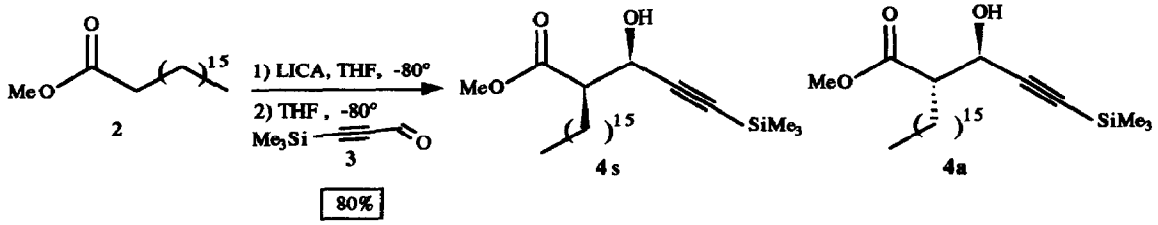


Scheme 2

In order to validate our strategy, we embarqued on the synthesis of one of the simplest member of this family of natural products, the *cis* 2-hexadecyl-3-hydroxy-4-methylene butyrolactone **1c**.[9] To our knowledge, the synthesis of this lactone has never been reported in the literature.[10] In this communication, we describe our synthesis of **1c** and of its *trans* isomer **1t** (Scheme 4). Since the natural product stereochemistry was mainly based on the coupling constant between the two adjacent protons in the 5-membered ring,[11] we realized the synthesis of both isomers, **1c** and **1t**, in order to unambiguously established the actual stereochemistry of the natural product.

With the selected strategy (Schemes 2-3), the first step required the addition of an enolate derived from stearic acid to the propargyl aldehyde protected at the triple bond. The trimethylsilyl group was the most convenient protecting group for the triple bond.[12] However, aldolisations involving silyl protected propargyl aldehyde derivatives proved to be scarce in the literature. In the two reports[13-14] dealing with such reactions, esters was used and in both cases, the enolates were obtained by deprotonation with LDA as a base. In our case however, with methyl stearate **2** as starting material, preliminary experiments[15] showed that LICA was more efficient than LDA as a deprotonating agent.

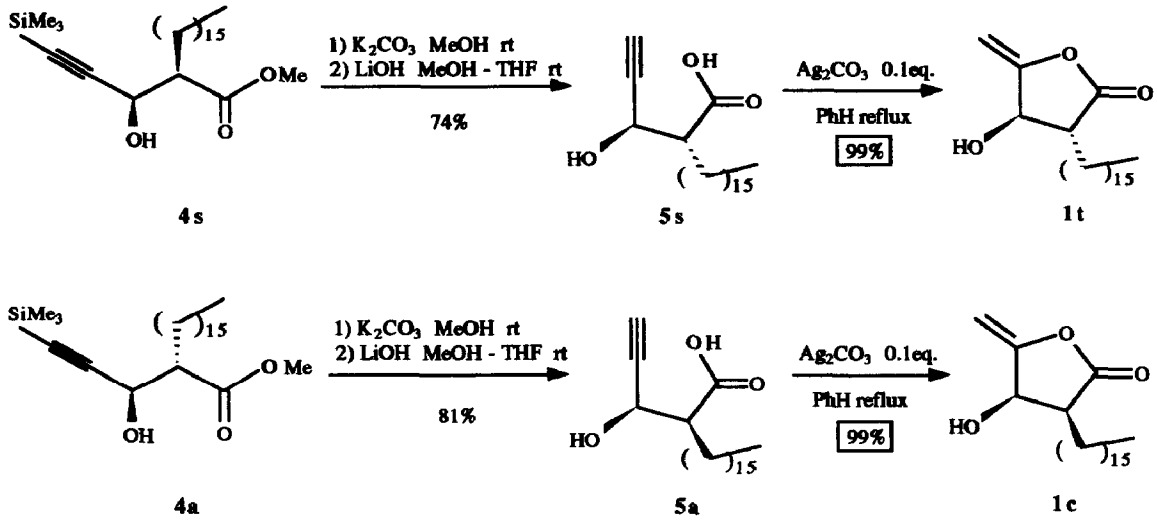
After generation with LICA in THF at -80°, the methyl stearate enolate was condensed to the 3-trimethylsilyl prop-2-ynal[16] **3** at -70°. After warming up and usual work up, a mixture of two diastereoisomers[17] **4** (53-47) was obtained (Scheme 3). Each diastereoisomer was conveniently obtained in pure form after flash-chromatography (combined yield : 80%). Their stereochemistry were easily determined using the ^1H NMR



Scheme 3

coupling constant between the protons at position 2 and 3.[18] The *syn* stereochemistry was assigned to the isomer exhibiting the lower coupling constant (J_{2-3} = 5.5 Hz) **4s** and the *anti* stereochemistry to the other isomer **4a** (J_{2-3} = 7.2 Hz).

Each diastereoisomer was then indepently deprotected (Scheme 4). The trimethylsilyl group was cleanly cleaved by potassium carbonate in methanol. Excess of lithium hydroxyde in a mixture of aqueous methanol and THF allowed for the formation of the free acetylenic acids **5a** and **5s** in good yields. Each acetylenic acid was then submitted to the standard conditions required for the silver-catalyzed cyclizations (Scheme 5).[3] When the *syn* diastereoisomer **5s** was treated with a catalytic amount of silver carbonate in refluxing benzene, a new less polar product rapidly formed. After 10 mn, filtration and solvent evaporation allowed to isolate this new product in quantitative yield. IR, ^1H and ^{13}C NMR spectroscopies unambiguously confirmed the expected cyclic structure for this compounds **1t**. Particularly characteristic were the exocyclic enol lactone data, with the methylene protons at 4.65 and 4.86 ppm, the lactone carbon at 174.27 ppm and the methylene carbon at 158.02 and 90.11 ppm The observed coupling constant between the two adjacent protons (H_2 and H_3) in the lactone ring was within the expected range[11] for a *trans* relationship of these protons (J_{2-3} = 5.9 Hz).



Scheme 4

With the *anti* isomer **5a**, we were expecting a less facile cyclization due to the fact that the cyclization would bring the alkyl chain and the hydroxyl substituent in a *cis* relationship. However, when submitted in the same conditions as the *syn* isomer, **5a** was converted to the cyclization product at only a slightly slower rate than **5s** was. The product **1c**, also isolated in nearly quantitative yield, proved to be spectroscopically identical to the natural compound.[8] This synthesis therefore confirmed the structure of the natural **1c**.

In conclusion, we have shown in this work that the silver-catalyzed cyclization of β-hydroxy-γ-acetylenic acids is an efficient method for the synthesis of β-hydroxy-γ-alkylidene-γ-lactones. Using a convergent strategy based on this method, we succeeded in the first total synthesis of the naturally occuring *cis*

2-hexadecyl-3-hydroxy-4-methylene butyrolactone, in 4 steps with an overall yield of 64%. Further developments are now in progress in our laboratory.

Acknowledgement: V. D. thanks the "Ministère de la Recherche et de la Technologie" for a doctoral fellowship. The authors thank Prof. J. Chuche, Université de Reims-Champagne-Ardenne, for his support and interest during this work.

References

1) For a revue of 4-ylidene butenolides and 4-ylidene tetronic acids, see: Pattenden, G. *Forschritte der Chemie Organischer Naturstoffe* **1978**, *35*, 133.
2) Vanwagenen, B. C.; Cardellina, J. H. *Tetrahedron* **1986**, *42*, 1117-1122, and references therein.
3) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447-6448.
4) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1988**, *29*, 2947-2950.
5) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1992**, *33*, 7857-7860.
6) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1992**, 33, 4905-4908.
7) Pale, P.; Bouquant, J.; Chuche, J. ; Carrupt, P. A.; Vogel, P. *Tetrahedron* submitted
8) For a recent review of related intramolecular electrophilic additions assisted by metallic salts, see: Larock, R. C.; Leong, W. W. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds; Pergamon: Oxford, 1991; vol. 4, pp. 269-327.
9) Ravi, B. N.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 105-112.
10) For synthesis of related natural compounds, see: Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560-564.
11) In 5-membered rings, the coupling constant between two adjacent protons is not characteristic enough to establish their relative stereochemistry; see: Jaime, C.; Segura, C.; Dinares, I.; Font, J. *J. Org. Chem.* **1993**, *58*, 154-158 and references therein.
12) Weber, W.P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; p. 129-158.
13) Dikshit, D. K.; Dingh, S. *Tetrahedron Lett.* **1987**, *29*, 3109-3110.
14) Guanti, G.; Baldaro, E.; Banfi, L.; Guaragna, A.; Narisana, N.; Valcavi, U. *Tetrahedron* **1988**, *44*, 3685-3692.
15) Dalla, V. DEA report, 1990, Université de Reims-Champagne-Ardenne. This work will be described in a forthcoming paper.
16) 3-trimethylsilylprop-2-yn-1-al was obtained in 3 steps from the propargylic alcohol: diprotection with trimethylsilyl chloride, selective hydroxyl deprotection with citric acid in methanol followed by oxydation .
17) No effort was attempted to improve the selectivity of this aldolisation since both isomers were required for further processing.
18) Heathcock, C. H. in *Asymmetric synthesis*; Morrison, J. D. Ed.; Academic Press: New York, 1985; vol. 3, p.115-118.

(*Received in France* 24 *February* 1994; *accepted* 24 *March* 1994)